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Clinical and Experimental Immunology

Clinical Immunology Review Series: An approach to the patient with recurrent superficial abscesses

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Summary

Patients may be referred to the immunology clinic for investigation of recurrent superficial abscess formation. In the majority of adult patients this clinical presentation does not equate with an underlying primary immune deficiency. Nevertheless, recurrent mucocutaneous abscesses can be associated with significant morbidity and long-term complications, including scarring and fistula formation, and may be associated with underlying immune-mediated disease. This review sets out an approach to the patient with recurrent superficial abscesses, focusing on the differential diagnoses, investigation and management of both the common causes and those associated with specific immune deficiency.

Keywords: abscesses, deficiency, immune, recurrent, superficial

Introduction

Recurrent mucocutaneous infection is a common clinical problem. The majority of cases are not due to an underlying primary immune deficiency. When considering immune deficiency, a distinction is made between rare primary causes and the much more common secondary causes; similarly, patients presenting with recurrent superficial abscess formation can be divided into those having a specific immune deficiency (the minority) from those with more common causes. The latter group includes patients with a wide spectrum of medical conditions, many being immune-mediated, encompassing staphylococcal skin carriage, chronic skin disease, diabetes mellitus (DM) and inflammatory bowel disease (IBD). Iatrogenic causes of secondary immune deficiency must be considered: for example, drug-induced leucopenia. Cutaneous ulceration may not be infective; additional differential diagnoses include venous insufficiency and pyoderma gangrenosum (PG). Psychogenic causes with factitious abscess formation, particularly if the pattern of disease is unusual, may need to be considered.

Where a primary immune deficiency is suspected, the differential diagnoses in paediatric and adult practice may vary, and may be determined by associated clinical features. The age at onset and pattern of disease, for example, can be discriminatory [1]. Onset of recurrent cutaneous abscesses in infancy may point immediately towards a neutrophil defect such as chronic granulomatous disease (CGD); however, adult onset does not exclude a primary phagocyte deficiency. The differential diagnoses of rash resembling atopic dermatitis in infancy associated with recurrent infection include hyper-immunoglobulin E (IgE) syndrome and, in males, Wiskott–Aldrich syndrome (WAS). One of the most important features of certain primary immune deficiencies is the relatively characteristic spectrum of disease-specific infections, which can help to focus the differential diagnosis. Careful attention to culture results can therefore guide further investigations. Phagocytic defects present generally at a young age with susceptibility to normally non-pathogenic bacteria and fungi, in contrast to T cell immunodeficiencies, where viral infection and candida are a particular problem. Mycobacterial infection, particularly with low-virulence mycobacteria, may point towards a defect in the type 1 cytokine pathway; see below. Failure to respond as expected to anti-microbial therapy raises the possibility of immune deficiency. The infection site may give clues, for example perianal or enterocutaneous abscess formation, suggesting underlying Crohn's disease rather than primary immune deficiency.

Table 1 sets out some pointers to aid in the differential diagnosis. When faced with the patient in clinic, the standard format of a careful clinical history and examination

Table 1. Useful clinical features in the differential diagnosis of recurrent superficial abscesses.

Clinical feature	Diagnostic utility
Age at onset	Paediatric onset may immediately suggest phagocytic or other primary immune deficiency
Underlying medical conditions	Higher rates of staphylococcal carriage and increased infection risk may result – see text
Family history	Positive family history may suggest an inherited primary immune deficiency, the inheritance pattern, e.g. X-linked or autosomal recessive, and details of consanguinity may guide diagnosis
Pattern of organ involvement	The pattern of organ involvement can be useful, e.g. skin, lung, liver and bone in CGD, apocrine gland bearing skin in HS, enterocutaneous fistulae in IBD
Organism	Atypical mycobacteria may suggest a defect in the type 1 cytokine pathway; invasive Aspergillus infection in CGD; *Pseudomonas otitis externa* in DM
Histology	Granuloma formation in IBD, CGD and MSMD; lack of infiltrating neutrophils in LAD

CGD, chronic granulomatous disease; HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; MSMD, Mendelian susceptibility to mycobacterial disease; LAD, leucocyte-adhesion deficiency syndrome-1.

focuses the differential diagnosis and guides appropriate investigation.

Common conditions associated with recurrent superficial abscesses

Staphylococcal carriage, chronic skin disease and cutaneous trauma

Humans are a natural reservoir of *Staphylococcus aureus*. Thirty to 50% of healthy adults are colonized, with 10–20% being colonized persistently [2,3]. The primary site of colonization is the nose, with the axilla, vagina, pharynx and damaged skin as additional sites. High colonization rates are found in patients with type 1 DM, intravenous drug users, patients on haemodialysis and in surgical patients. Staphylococcal colonization is known to increase the risk of infection resulting from breaches in the skin or mucous membrane barrier. Leucocytes are the primary host defence against *S. aureus* and the typical pathological finding of staphylococcal disease is abscess formation. Patients with quantitative or qualitative defects in leucocyte function are therefore at increased risk of staphylococcal disease (phagocytic immune deficiencies are discussed below). Strains of *S. aureus* harbouring the *lukS-lukF* gene encoding the Pantin–Valentine leucocidin (a leucocytotoxic toxin) are frequently associated with severe furunculosis in individuals with no known immune deficiency [4].

The combination of chronic skin disease, skin trauma and staphylococcal carriage increase the risk of abscess formation; atopic eczema is a good example. Injection drug users are at increased risk of abscess formation because of the increased rates of staphylococcal carriage and recurrent epithelial breaches. Although a primary immune deficiency is unlikely in this context, secondary immune deficiency, specifically human immunodeficiency virus needs to be considered and the opportunity taken for testing. Abstinence from injection drug use and hygiene measures are critical.

Treatment of staphylococcal carriage is set out in Table 2.

Diabetes mellitus

The association of recurrent infection with diabetes is well recognized, diabetes being classified by the World Health Organization as a cause of secondary immune deficiency [5]. The association between diabetes and increased susceptibility to infection in general is not supported by strong evidence; however, certain infections are more common in patients with diabetes: for example, group B Streptococcal bacteraemia, tuberculosis (TB) and mucocutaneous candidiasis, while others occur almost exclusively in this context: for example, rhinocerebral mucormycosis [6]. In addition, certain infections, e.g. TB, mucocutaneous candidiasis and cellulitis, may be more severe. Staphylococcal carriage rates are higher in DM.

Diabetes impairs several aspects of host defence, the prevalence of infection correlating with glycaemic control. Polymorphs show functional alterations in chemotaxis and phagocytosis [7], with reduced chemotaxis most marked when glycaemic control is poor. The killing activity of polymorphs is also depressed by hyperglycaemia. The four most important elements associated with increased infection risk are the underlying susceptibility to infection, vascular disease, nerve damage and hyperglycaemia. Vascular insufficiency and tissue hypoxia allow the growth of anaerobic organisms and limit host defence mechanisms. Neuropathy

Table 2. Treatment of cutaneous staphylococcal carriage [4].

A stringent 5-day decolonization regime including:
- Mupirocin nasal ointment three times daily
- Hand disinfection with an alcohol-based antibacterial after application of the nasal ointment
- Daily treatment of the skin and hair with an octenidin-based wash solution
- Antiseptic treatment of the throat with 0·1% chlorhexidine gargle three times daily
- Daily disinfection of personal items, bath or shower with an alcohol-based anti-microbial cleanser
- Daily changing and washing (at a temperature of at least 60 degrees) of towels, bedclothes, underwear and clothing

can alter pressure distributions contributing to ulceration, particularly relevant for foot infection. Microangiopathy may prevent adequate antibiotic penetration, leading to persistent infection. Soft tissues and skin are frequent targets, foot infection being the most common [6], with necrotizing fasciitis potentially one of the most serious. Nephrotic syndrome, with urinary IgG loss, is an additional consideration.

Good metabolic control is a major factor in limiting the development and spread of infection, and more importantly the development of complications that predispose to infection [7,8]. Diagnosis is straightforward from routine biochemistry, if not already known. Management involves good metabolic control, foot care, early and aggressive management of infection, which may include surgical debridement or amputation. Diabetes is a risk factor for hidradenitis suppurativa (HS). The association with myeloperoxidase deficiency is discussed below.

Hidradenitis suppurativa

Hidradenitis suppurativa is a common disorder of the apocrine gland-bearing follicular epithelium, affecting predominantly the axilla, perineum and groin, with a prevalence of up to 4·1% [9]. Follicular hyperkeratosis, leading to occlusion and follicular rupture, with inflammation and sometimes secondary infection, is thought to give rise to the clinical findings. It is more common in females than males, reported ratios varying from 2 : 1 to 5 : 1. Although it may develop in any skin bearing apocrine glands, genitofemoral lesions tend to be more common in females; axillary involvement shows less of a gender predilection. It is a recurrent disorder with a variable clinical course; scarring, functional impairment and rarely malignant change may result. It usually develops in otherwise healthy post-pubertal individuals. A recent study reported a reduction in the percentage of natural killer cells over time and a lower monocyte response to bacterial components in patients with HS [10]. A genetic predisposition is likely, 26% of patients having a family history; however, a specific genetic locus has yet to be determined. Risk factors include diabetes and smoking. The influence of hormones remains controversial. Obesity, although not causal, may aggravate HS, as may tight clothing, poor hygiene, deodorant and chemical depilation.

Diagnosis is largely clinical. Tender papules or deep nodules develop in affected areas. These may resolve slowly, but often expand and coalesce with surrounding nodules to form a large, painful inflammatory abscess, which may rupture spontaneously. Lesions can heal with fibrosis and sinus tracts can develop. Routine cultures are often negative, but bacteria recovered from HS lesions most frequently include *S. aureus* and coagulase-negative staphylococci.

Complications may be local, resulting in scar formation, or systemic including sepsis. There is an association with acne conglobata and dissecting cellulitis of the scalp; the latter, also known as perifolliculitis capitis abscedens et suffodiens, manifests as perifollicular pustules, nodules, abscesses and sinuses evolving into scarring alopecia.

Medical treatment includes early antibiotics, topical antiseptics and compresses. Intralesional steroid can be considered for an isolated number of tender lesions. Isotretinoin monotherapy is of limited benefit, while other systemic retinoids have demonstrated some efficacy. Monoclonal antibody therapy is now being investigated following the report of efficacy in a patient with Crohn's disease and axillary HS [11]. A retrospective study reported by Sullivan *et al*. in 2003 [12] suggested that infliximab is a promising agent. Etanercept has been used with some success in small numbers of patients [13]. Other systemic immune suppression has been used with varying success, e.g. azathioprine and cyclosporin. Hormonal treatment, cyproterone acetate with ethinyloestradiol, has been applied, as has Finasteride [9]. Surgical excision or carbon dioxide laser ablation are the most effective treatment modalities, with healing by secondary intent. A more conservative surgical approach, with de-roofing or marsupialization, may be appropriate in limited cases. A recent report of 106 cases referred to a regional plastic surgery unit found that primary closure had a recurrence rate requiring at least one secondary operation of 69·88% [14]. No recurrence, serious complication or revision surgery was required in the group undergoing graft or flap surgery. The report concluded that HS should be treated aggressively by radical excision of all hair-bearing areas and reconstructed with a graft or flap. Incision and drainage leads almost invariably to recurrence and should be reserved for small single purulent lesions. Close liaison with surgical colleagues is important.

Inflammatory bowel disease

The reported incidence of dermatological manifestations in IBD vary from 1–15% of patients [15] to up to 20% in patients with Crohn's disease [16], with a higher incidence when the colon is involved. Erythema nodosum and PG are the most common cutaneous manifestations. Erythema nodosum is unrelated to the extent or severity of the disease but is related to disease activity and generally responds to treatment of the underlying disease. PG is associated with more severe bowel disease and may require treatment in its own right; see below.

Crohn's disease is complicated by the development of fistulas in approximately one-third of patients. These may be internal, e.g. bowel to bladder, or enterocutaneous, involving the abdominal wall or perineum. Such cases may present as cutaneous abscess. The response to standard treatment is poor, and surgery may be required. Immunomodulatory treatment with infliximab has an established role in fistulizing Crohn's disease [17,18]. Symptoms of IBD should be sought specifically from the clinical history.

Table 3. Laboratory investigations to consider in the diagnosis of recurrent superficial abscesses formation.

Laboratory investigation	Specific features
FBC	White cell differential – neutropenia or lymphopenia, platelet count – thrombocytopenia
Blood film	Abnormalities in neutrophil or platelet morphology and platelet size (microthrombocytopenia in WAS)
IgE	Elevated in atopic eczema, very high levels may suggest hyper-IgE syndrome
CRP	Evidence of active infection or ongoing inflammation (IBD)
Blood glucose	Diabetes confirmation
Microbiology	Staphylococcal carriage/MRSA screen, culture and PCR of lesional tissue
Histology	White cell infiltration (absence in LAD), granuloma formation (maturity thereof in MSMD)
Neutrophil function	Metabolic burst by flow cytometry (Fig. 1) or nitroblue tetrazolium reduction (NBT) test – CGD
Neutrophil phenotyping	Adhesion molecule expression by flow cytometry – LAD
Lymphocyte phenotyping	Surface expression of B, T and NK cell markers (may identify CD4 lymphopenia or HIV infection, for example)
IFN-γ/IL-12 pathway analysis	To identify patients with MSMD
Specific protein expression and genetic analysis	For specific primary immune deficiency diagnosis via specialist referral laboratory
HIV, hepatitis B and C (HCV) status	In injection drug users presenting with recurrent superficial abscesses
Renal function	Particularly in patients with diabetes and HCV infection
C4 and cryoglobulin	If cryoglobulinaemia a potential complicating factor, e.g. in HCV infection

CGD, chronic granulomatous disease; CRP, C-reactive protein; FBC, full blood count ; IFN, interferon; IL, interleukin; IgE, immunoglobulin E; HIV, human immunodeficiency virus; NK, natural killer; MRSA, methicillin-resistant *Staphylococcus aureus*; MSMD, Mendelian susceptibility to mycobacterial disease; WAS, Wiskott–Aldrich syndrome; PCR, polymerase chain reaction; LAD, leucocyte-adhesion deficiency syndrome-1; IBD, inflammatory bowel disease.

Primary immune deficiencies associated with recurrent superficial abscesses

Chronic granulomatous disease

Chronic granulomatous disease is an inherited immune deficiency caused by defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, the enzyme complex that generates superoxide in phagocytes [19–26]. The estimated US incidence is one in 200 000 live births [25]. It is characterized by recurrent life-threatening infection caused by catalase-positive bacteria and fungi, granulomatous inflammation and autoimmune manifestations [27]. The NADPH oxidase is composed of a membrane-bound heterodimer of $gp91^{phox}$ and $p22^{phox}$ within the membrane of secondary granules, and four cytosolic proteins, $p47^{phox}$, $p67^{phox}$, $p40^{phox}$ and rac, all of which are required for full oxidase activity. Generation of superoxide activates the primary granule proteins neutrophil elastase and cathepsin G, which are necessary for microbial killing [25]. CGD can be caused by mutations in any of the four structural genes of the NADPH oxidase, $gp91^{phox}$, $p22^{phox}$, $p47^{phox}$ or $p67^{phox}$. The majority of cases are X-linked recessive, caused by mutations in $gp91^{phox}$; the remainder are autosomal recessive. The majority of patients are diagnosed in infancy/childhood on the basis of recurrent infection or granulomatous disease. The skin, lymph nodes, lungs, liver and bones are frequent infection sites [19,25,28]. A limited number of pathogens are reported, particularly *S. aureus*, *Burkholderia cepacia*, *Serratia marcescens*, Nocardia and Aspergillus species [1,25]. *Chromobacterium violaceum* is a rare cause of life-threatening bacteraemia in CGD. A recently reported Gram-negative bacterium, *Granulobacter bethesdensis*, has been associated with severe chronic necrotizing deep lymphatic infections [27].

Chronic granulomatous disease neutrophils produce more interleukin (IL)-8 than normal neutrophils, suggesting an essential feedback in which oxidants normally curtail inflammation by limiting IL-8 production. CGD neutrophils also have delayed apoptosis, interrupting the normal process that prevents tissue damage at sites of inflammation from necrotic lysis and proteases released from dying neutrophils. Both factors may contribute to the granulomatous inflammation [27]. Absence of active NADPH oxidase in T lymphocytes appears to cause a shift in T cells to a T helper 1 (Th-1) cytokine pathway on activation which may explain, in part, the increased risk of certain Th-1 autoimmune disorders in CGD patients.

Despite the fact that most patients will present with typical clinical features at a young age, late presentations have been reported [29–31] and do not appear to discriminate between the specific genetic defects. CGD should therefore be considered in any patient with recurrent superficial infection caused by the above organisms, particularly if there is a history of additional invasive bacterial or fungal infection, or granulomata.

Diagnosis by assessment of the neutrophil metabolic burst using flow cytometry is straightforward (Table 3 and Fig. 1), with confirmation by subsequent genetic analysis. Implications regarding family screening and prenatal diagnosis will not be discussed here.

Management includes appropriate antibiotic and antifungal prophylaxis – cotrimoxazole and itraconazole, aggressive pharmacological therapy and, if appropriate, surgical

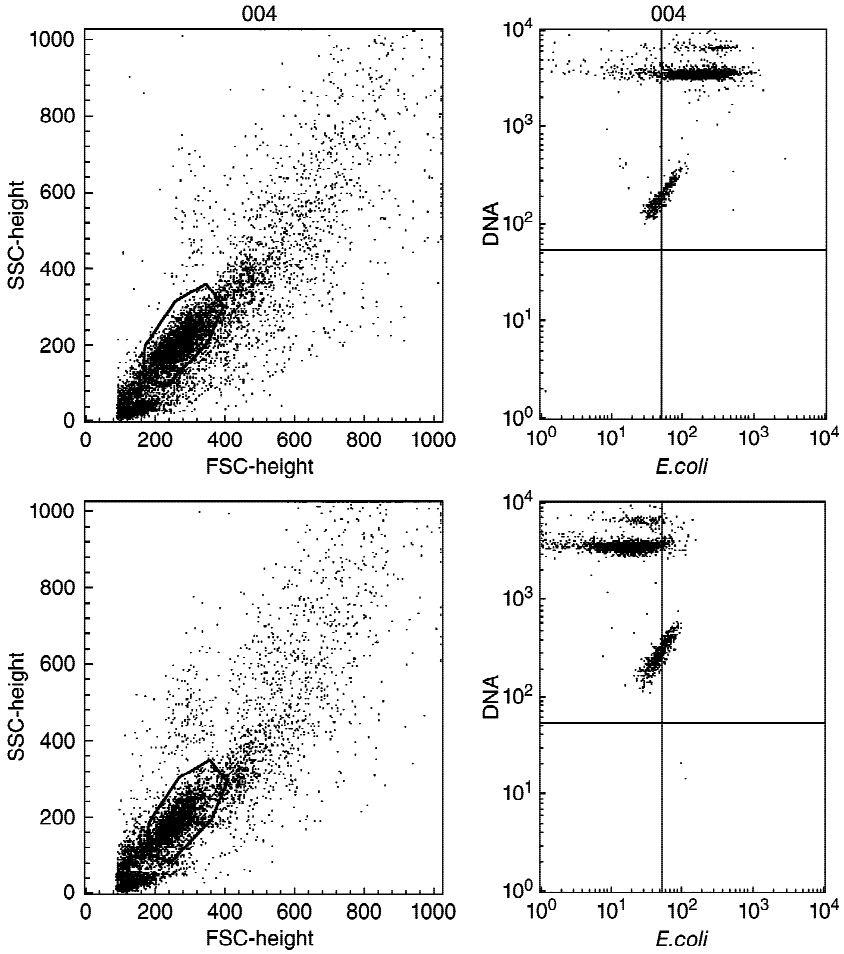

Fig. 1. Flow cytometry in chronic granulomatous disease (CGD). The upper two flow plots represent the control sample, with evidence of a normal metabolic burst following granulocyte phagocytosis of opsonized *Escherichia coli* (dihydrorhodamine oxidation – upper right second panel). The lower panels represent the lack of metabolic burst obtained from a patient with autosomal recessive CGD.

intervention for invasive infection, consideration of interferon (IFN)-γ and neutrophil infusions [28,32–36]. There are reports on the successful use of the newer anti-fungal agents, caspofungin and voriconazole, in otherwise refractory fungal infection [37,38]. Non-myeloablative haematopoietic stem cell transplantation can be definitive treatment if a suitable donor is available [39], and data are emerging regarding gene therapy [27]. Specialist referral is required for such treatment.

Leucocyte adhesion molecule deficiency

Several molecular defects of leucocyte adhesion cause recurrent life-threatening infection. Leucocyte-adhesion deficiency syndrome-1 (LAD-1), an autosomal recessive disorder, results from mutations in the common chain of the β_2 integrin family, CD18, affecting the β_2 integrin heterodimers CD11a/CD18, CD11b/CD18 and CD11c/CD18. As CD18 is required for normal expression of these heterodimers, defects lead to either very low-level or absent expression [25]. Neutrophils are unable to aggregate, bind to intercellular adhesion molecules on endothelial cells and to migrate to sites of infection/inflammation. Even in the absence of infection the peripheral blood neutrophil count is elevated.

Leucocyte-adhesion deficiency syndrome-1 usually presents with recurrent severe infection, impaired pus formation and impaired wound healing. Patients with the severe phenotype have delayed umbilical cord separation, omphalitis, persistent leucocytosis, severe destructive gingivitis and periodontitis leading to tooth loss and alveolar bone resorption. Recurrent infection of the skin is usually caused by *S. aureus* or Gram-negative bacilli. Lesions tend to necrotize and ulcerate. Typically, little surrounding inflammation is seen and there is almost complete absence of neutrophils in biopsy material. The moderate phenotype, with expression levels in the order of 1–30% of normal, is milder and tends to be diagnosed later in life. Delayed wound healing is still the rule [25]. A patient labelled as having PG was later shown to have moderate LAD-1 deficiency [40], confirmed on flow cytometry and genetic analysis. LAD-1 therefore needs to be considered in the context of recurrent cutaneous infection, particularly if the histology is suggestive. More than 40 mutations have been identified [27].

Leucocyte-adhesion deficiency syndrome-2 is a very rare autosomal recessive disorder caused by an inborn error of

fucose metabolism, resulting in absence of fucosylated glycans at the cell surface [27]. It leads to impaired expression of Sialyl Lewis X (CD15s) and other fucosylated proteins that function as selectin ligands. It is caused by mutations in the guanosine diphosphate–fucose transporter [24,25]. Additional features include mental retardation, skeletal anomalies, distinctive facies and the Bombay blood phenotype. The infection pattern resembles that of the moderate phenotype of LAD-1, but infection frequency and severity are reported to decrease with age [25].

Leucocyte-adhesion deficiency syndrome-3 has been described in four patients with recurrent infection and a bleeding disorder, characterized by general failure to activate a number of integrins in response to cytokines. The defect is as yet unclear, but one case had an abnormality of Rap-1 function, a regulatory GTPase involved in regulation of integrin signalling [24,27]. Rac 2 deficiency has also been described as a cause of LAD [25].

Non-myeloablative stem cell transplantation has been successful treatment for LAD; gene therapy may be a future option. As for CGD, specialist referral for definitive treatment is required.

Mendelian susceptibility to mycobacterial disease

In 1998, Casanova *et al*. reported on recessive mutations in four genes, encoding IFN-γR1, IFN-γR2, IL-12 p40 and IL-12Rβ1 as a cause of disseminated infection with bacille Calmette–Guérin (BCG), non-tuberculous mycobacteria and, in some cases, Salmonella [41]. Patients are also vulnerable to *Mycobacterium tuberculosis*. Impaired IFN-γ-mediated immunity was presumed to be the common mechanism. The severity of the phenotype was found to be dependent upon the specific defect. Complete IFN-γR1 and IFN-γR2 deficiency predisposes to overwhelming infection, with impaired granuloma formation in early childhood, and is associated with lack of response to high-dose IFN-γ. Partial IFN-γR1 deficiency and complete IL-12 p40 and IL-12Rβ1 deficiencies are associated with curable infections, with mature granulomas at various ages [41,42]. Defects in signal transducer and activator of transcription 1 (STAT1) have since been reported; mutations in the five disease-causing autosomal genes account for at least 12 distinct genetic disorders [43]. More recently two X-linked recessive forms of mendelian susceptibility to mycobacterial disease have been reported, one involving NEMO, the specific defect in the second group as yet unidentified, herpes zoster in early adulthood being noted in the latter group [43].

Patients with the severe phenotypes present early in life with disseminated severe infection, especially if they have received BCG vaccination. Multi-focal mycobacterial osteomyelitis in a child or young adult raises the question of autosomal dominant (AD) IFN-γR1 deficiency [25]. In the context of recurrent superficial abscess formation, a defect in this pathway will need to be considered if there is adenitis and skin fistulization following BCG vaccination or fistulizing lymphadenopathy. The histology may be instructive. In patients with AD IFN-γR1, IL-12 p40 or IL-12Rβ1 defects, IFN-γ is effective with anti-microbials. Bone marrow transplantation for IFN-γR defects need to be considered carefully, mortality being high in the context of active infection.

Mycobacterial infection in the context of secondary immune deficiency

Mycobacterial skin disease may present as recurrent cutaneous nodules, requiring biopsy for diagnosis. *M. chelonae* skin abscesses have been reported in the context of renal transplantation, for example [44], and cutaneous metastatic tuberculous abscess with underlying lymphoma [45]. Such cases highlight the need for careful histopathological and microbiological assessment of patients with unusual skin manifestations and underlying primary or secondary immune deficiency.

Severe congenital neutropenia

Severe congenital neutropenia (SCN) is characterized by profound neutropenia resulting from failure of promyelocytes to mature into myelocytes. It usually presents within the first year of life. Infections include cellulitis, perirectal abscess, peritonitis, stomatitis and meningitis, *S. aureus* and Burkholderia species being common isolates. Some patients have acquired mutations in the myeloid lineages and are at risk of myelodyplastic syndrome and acute myeloid leukaemia [19,26]. Mutations in the genes encoding elastase 2 (ELA2), growth factor 11 and granulocyte–colony-stimulating factor receptor have been identified to date [24]. Cutaneous infection can be a feature of the Shwachmann–Diamond syndrome, characterized by exocrine pancreatic dysfunction, skeletal abnormalities, bone marrow dysfunction and recurrent infection [19,26]. In almost all patients with SCN treatment with granulocyte–colony-stimulating factor results in significantly fewer infections.

Hyper-IgE syndrome

Eczema, abscesses, candidiasis, pneumonia, eosinophilia and elevated levels of serum IgE were the most common immunological features reported in 30 patients with the hyper-IgE syndrome [46]. Cold abscesses, with boils reported in 87% [47], and candidiasis are the most common cutaneous infections. These patients have difficulty in mounting an adequate immune response to *S. aureus*. Some of the earliest data implicated abnormal neutrophil chemotaxis and an altered immunoglobulin profile as the primary immune defect. Missense mutations and single-codon in-frame deletions in *STAT3* have been reported very recently in 50 familial and sporadic cases of the hyper-IgE syndrome as the causative defect. Eighteen discrete mutations, five of which

were hot spots, were predicted to directly affect the DNA binding and SRC homology 2 domains of STAT3 [48]. Diagnosis is important, as ongoing antibiotic prophylaxis is required to reduce the associated staphylococcal lung infections and risk of pneumatocoele development.

Primary immune deficiencies associated with recurrent superficial infection

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome is a rare X-linked primary immune deficiency characterized by eczema, thrombocytopenia and progressive combined immune deficiency. The WAS protein gene encodes a cytoplasmic protein whose expression is restricted to haemopoietic stem-cell derived lineages. The protein is crucial to cell polarization, migration and phagocytosis [49]. The variability of the clinical phenotypes correlates with the mutations in the WAS protein gene [50]. Recurrent cutaneous infection can result from staphylococcal carriage, the chronic skin disease, the underlying immune deficiency which can include neutropenia and systemic immune suppression that may be required to treat the skin disease. WAS is an important differential diagnosis to consider in male children presenting with severe infected eczema, as bone marrow transplant may be curative. The best transplantation outcomes are achieved with human leucocyte antigen (HLA)-identical sibling donors, but boys undergoing unrelated donor transplantation before the age of 5 years have survival similar to those receiving HLA-identical sibling transplants [51]. Gene therapy is likely to be a future option.

Other neutrophil disorders

Cyclic neutropenia

Cyclic neutropenia is an AD disorder in which cyclic haematopoiesis causes intervals of neutropenia and susceptibility to opportunist infection [26]. A typical cycle is 21 days' duration, with severe neutropenia lasting for 3–6 days of this. Cycle length is, however, variable. Although this may be asymptomatic, during the period of severe neutropenia patients may develop aphthous ulcers, gingivitis, stomatitis and cellulitis. Mutations in the neutrophil elastase gene 2 (ELA2) have been identified [24].

Other causes of neutropenia include CD40 ligand deficiency and WAS [1].

Specific granule deficiency

A few patients have been found to have abnormal neutrophils with bilobar nuclei, in which the specific granules are incompletely formed. A chemotactic defect has been described. Clinically, cases present with increased frequency of severe skin and pulmonary infections, with *S. aureus*, *S. epidermidis* and enteric bacteria being the most common isolates. The molecular defect is unknown [19,26].

Myeloperoxidase deficiency

This is the most common inherited disorder of neutrophils and includes complete deficiency, structural or function enzyme defects. Deficiency is not usually associated with

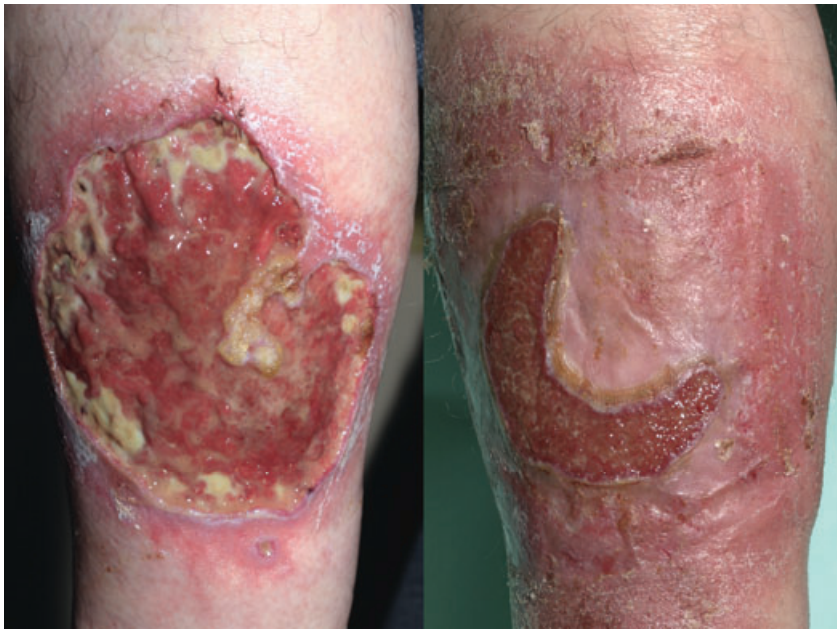

Fig. 2. Pyoderma gangrenosum (PG). The left panel shows a large PG lesion from the lower limb of a patient with rheumatoid arthritis that failed to respond to steroid and cyclosporin. The right panel shows improvement with high-dose intravenous immunoglobulin and tapering steroid (contact sensitivity investigations are pending for the surrounding erythema in the right panel).

disease except in patients with DM, who are susceptible to disseminated candida infection [26].

Other conditions associated with recurrent superficial ulceration

Non-infectious neutrophilic dermatoses

Such disorders may need to be considered in the context of recurrent superficial infection. The differential diagnosis of Sweet's syndrome, for example, includes bacterial sepsis, cellulitis, erysipelas, herpes simplex infection, syphilis and PG [52].

Pyoderma gangrenosum

Pyoderma gangrenosum is a rare non-infectious neutrophilic dermatosis characterized by recurrent painful cutaneous ulceration. Lesions of PG start generally as sterile pustules that progress rapidly into painful ulcers of variable depth and size. Secondary infection is a risk. The legs are the most common site, but other skin areas and mucous membranes can be affected (Fig. 2). PG is associated with an underlying systemic disease in about 50% of cases, most commonly IBD, rheumatic or haematological disease [53]. Patients may present to the clinic because of concern regarding an underlying immune disorder or for advice concerning immunomodulatory therapy, for example cyclosporin, high-dose intravenous immunoglobulin [54] or anti-tumour necrosis factor treatment [15,55]. The diagnosis is largely clinical, with support from histology and exclusion of differential diagnoses (vascular occlusive disease, vasculitis, malignancy, infection, trauma and drug reactions).

Summary

The differential diagnosis of patients presenting with recurrent superficial abscesses is broad; the majority of cases are not associated with an underlying primary immune deficiency. The principle role of the immunologist is to recognize patients with a specific immune deficiency and direct appropriate investigation and management, including referral for definitive treatment in those rare cases where bone marrow transplantation or gene therapy may be curative. A secondary role is in guidance concerning immunomodulatory therapy in cases where recurrent superficial infection or ulceration is a manifestation of underlying immune mediated disease.

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